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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/554,314	04/19/2006	Christoph Hock	78247/JPW/YC	2670

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EXAMINER
WANG, CHANG YU

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
12/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/554,314	HOCK ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7 and 11-18* is/are pending in the application.

4a) Of the above claim(s) *11-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-7 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/2/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/2/08 has been entered.

Status of Application/Amendments/claims

2. Applicant's amendment filed 10/2/08 is acknowledged. Claims 2-3 and 8-10 are cancelled. Claims 1, 5-7 are amended. Claims 1, 4-7, and 11-18 are pending in this application. Claims 11-17 are withdrawn without traverse (the response filed on 6/1/07) from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Claims 1, 4-7 and 18 are under examination in this office action.

4. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response.

5. Applicant's arguments filed on 10/2/08 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Information Disclosure Statement

6. On p. 5 of the response, Applicant request the examiner clearly indicate which references have been considered to comply with MPEP 609.05 or 609.08 because the returned PTO-1449 was only indicated "all references considered except where lined through".

In response, based on MPEP § 609.01 [R-7]-(A) with regard to e-IDS & § 609.08, Electronic processing of IDS, the examiner's action has complied with MPEP. As indicated in the returned IDS mailed 5/28/08, all of the references were considered except the lined-through one, which was EP1172378 because it was cited in PTO-892 mailed 5/3/07. See MPEP § 609.08 with regard to electronic processing of IDS.

"As of October 1, 2007, examiners may use an alternative electronic signature method for IDS. Under the alternative electronic signature, examiners will no longer initial each reference citation considered, but will continue to strikethrough each citation not considered. Each page of reference citations will be stamped by the examiner with the phrase "All references considered except where lined through" along with the examiner's electronic initials, and the final page of reference citations will include the examiner's electronic signature.".

Claim Rejections/Objections Maintained

6. The rejection of claims 1, 3-7 and 18 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in response to Applicant's amendment to the claims and cancellation of claim 3.

Claim Rejections/Objections Maintained

In view of the amendment filed on 10/2/08, the following rejections are maintained.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-7 and 18 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting an increased level of immunostaining on brain sections of $APP^{SW}xPS1^{M146L}$ double-transgenic mice or increased levels of antibodies against β-amyloid in serum and CSF samples of Alzheimer disease (AD) patients who are immunized with Aβ peptides, AN1792(QS-21), and detecting a positive correlation between the increased immunostaining and improvement of immunization treatment in AD patients, does not reasonably provide enablement for a method of monitoring an immunotherapy in a subject suffering from Alzheimer's disease by contacting all types of test samples with all forms of amyloid plaque (including all fragments, derivatives or mutants) in all types of tissue sections and comparing the level of immunoreactivity to an undefined reference value of AD as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The rejection is maintained for the reasons made of record.

On p. 6-9 of the response, Applicant argues that amended claims are enabled because independent claim 1 has been amended to recite a brain section containing β-amyloid plaques. Applicant also argues that any brain section can be used for an antibody containing test sample in the claimed method as long as the brain section

contains β-amyloid plaques. Applicant further cites Hock et al. (Neuron 2003, 38: 547-554, Exhibit 1), Wang et al. (J. Alzheimer's Disease, 2008, 14: 161-173, Exhibit 2), WO2007/022416 (Exhibit 3) and Sabamuri et al. (J. Alzheimer's disease, 2008, 14: 175-177, Exhibit 4). On p. 10 of the response, Applicant argues that the rejection is obviated because claim 7 has been amended to recite "non-human animal is transgenic for human APP or a mutant thereof". Applicant's arguments have been fully considered but they are not persuasive.

In contrast, the limitation of "a test sample" recited in independent claim 1 is not limited to "an antibody containing test sample" that can immunoreact with brain sections containing β-amyloid plaques. In fact, the recitation of "a test sample" encompasses any samples including different tissues or body fluids with or without an antibody. However, based on the specification, only serum or CSF samples of Alzheimer disease (AD) patients who are immunized with Aβ peptides, AN1792(QS-21), can be used in the claimed method to be detected against brain sections of $APP^{SW}xPS1^{M146L}$ double-transgenic mice. In addition, as previously made of record, immunizing a subject with an amyloid component such as tau protein will not generate an antibody against APP or a mutant thereof as recited in claim 7 because immunization with tau will result in generation of anti-tau antibodies, which will not immunoreact with APP or its mutants. Further, neither the instant specification nor the prior teaches that immunization with other β-amyloid components other than Aβ1-42 peptides would have immunotherapeutic effects in AD. Thus, it is unpredictable whether all of the β-amyloid components can be used in the claimed method.

Furthermore, it is known in the art that each antibody can only bind to a specific set of epitopes. If the epitopes of a brain section containing β-amyloid plaques do not match the epitopes that were raised to generate antibodies, then the brain section cannot be used for detecting the antibodies. In this instant case, the recitation of "a brain section containing β-amyloid plaques" is not limited to brain sections containing epitopes that can be recognized by antibodies generated from immunization with Aβ peptides, AN1792(QS-21). The instant specification fails to teach whether all of brain sections from different species or derived from different mutants (as recited in instant claim 7) contain the same epitopes as those of the brain sections derived from brain sections of $APP^{SW}xPS1^{M146L}$ double-transgenic mice. The instant specification also fails to teach whether the epitopes within different brain sections containing β-amyloid plaques can be recognized by antibodies generated from different Aβ peptides or other components of β-amyloid as recited in instant claim 1. There is no teaching of a correlation between different epitopes within different brain sections and the epitopes within the brain sections of $APP^{SW}xPS1^{M146L}$ double-transgenic mice. Thus, it is unpredictable whether all of the brain sections can be used in the claimed method to monitor or prognosticate the clinical outcome of an immunotherapy in a subject suffering from AD and being immunized with any β-amyloid component as currently claimed.

As previously made of record, the scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, it is unpredictable whether all of different brain sections derived from different mutants can be used in the claimed method, and the experimentation left

to those skilled in the art is extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed invention as currently claimed without further undue experimentation. Note that

"The 'predictability or lack thereof' in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971)" See MPEP § 2164.03

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 4-7 and 18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Dodel et al. (EP1172378, published on Jan 16, 2002 as cited in the previous office action) in view of Schenk et al. (Nature. 1999. 400: 173-177). The

rejection is based on the subject matter that is enabled within the claims as set forth in section of *Claim Rejections - 35 USC § 112.* The rejection is maintained for the reasons made of record.

On p.12-14 of the response, Applicant argues that applied references do not render the claimed method obvious. Applicant argues that although Dodel teaches the detection of the levels of anti-Aβ antibodies and Aβ in plasma and CSF, Dodel teaches therapeutic treatment to decrease β-amyloid in CSF by an Aβ/anti-Aβ complex and does not teach use of a β-amyloid plaque-containing brain section for detecting the anti-Aβ antibody following a respective dose of IgG immunization. On p. 14-17 of the response, Applicant also argues that Schenk does not render the claimed because Schenk only teaches use of brain tissue sections to determine whether there is a reduction of amyloid plaque load. Applicant argues that neither Dodel nor Schenk teaches use of a brain section containing β-amyloid plaques to determine the level of immunoreactivity of the test sample with β-amyloid plaques present in the amyloid amyloid plaque-containing tissue section. Applicant's arguments have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In contrast, the examiner asserts that the combined references do render the claimed method obvious. Briefly, Dodel (EP'378) teaches detection of the levels of anti-Aβ antibodies and Aβ peptides in plasma and CSF as in instant claims 1, 4 and 18 as compared to controls or before treatment (i.e. comparing the level of immunoreactivity between a test sample and an amyloid plaque-containing sample as in claims 1, 4, 8 and 18; see col.3 [0019]; col. 6 [0038]). Although Dodel does not teach contacting serum or CSF with a brain section containing amyloid-plaques or derived from non-human transgenic mice, the use of a brain section containing amyloid-plaques to monitor immunotherapy is obvious because Schenk teaches detection of an reduction of amyloid plaque by immunohistochemical staining on the brain sections of these immunized mice as compared to those of non-immunized PDAPP mice (see p. 176-177). The detection of reduced amyloid plaques in immunized PDAPP mice as compared to non-immunized mice indicates that the antibodies generated from Abeta immunization can recognize amyloid plaques and thus there is a higher level staining in non-immunized mice. Schenk also teaches detection of increased levels of anti-Abeta antibodies in serum or CSF of transgenic PDAPP mice immunized with Abeta peptides. Although Schenk does not directly use brain sections of non-immunized PDAPP mice to detect the levels of anti-Abeta antibodies in immunized mice, it is expected to detect higher levels of amyloid-plaques on brain sections derived from non-immunized transgenic animals and use as an indicator because the levels of anti-Abeta antibodies from patients or animals with Abeta immunization are increased in serum and CSF, and can recognize the epitopes of Aβ (immunogen) on the brain sections of non-immunized

transgenic PDAPP animals (amyloid-plaque containing tissue sections). Thus, the increased immunoreactivity as compared to prior to immunotherapy on brain sections containing human amyloid-plaques (PDAPP) is expected when contacted with the serum or CSF derived from animals or patients immunized with Abeta and thus to monitor the efficacy of immunotherapy.

Accordingly, the claimed method as recited in instant claims are obvious over the applied references because animals or patients immunized with Aβ generate anti-Aβ antibodies against Aβ plaques and show reduced Aβ burden. Thus, a skilled artisan would have expected success in monitoring an immunotherapy in a subject suffering from AD by using brain sections of transgenic animals containing amyloid plaques as a tool to detect the anti-Abeta level after immunization because detection of higher levels of amyloid-plaques on brain sections of PDAPP mice is expected and the increased level of anti-Abeta antibodies in AD immunized with Abeta has been shown to reduce Abeta burden as taught by Schenk Dodel, which is as an indicator of improvement of the immunotherapy in AD.

Note that it would have been obvious by combining prior art elements according to known methods to yield predictable results because all the claimed elements were known in the prior art and one skilled in the art could have arrived at the claimed invention by using known methods, which is applied to the instant application. In addition, it is also obvious by applying a known technique to a known product ready for improvement to yield predictable results because a particular known technique was recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary

skill in the art would have been capable of applying this known technique to a known product that was ready for improvement and the results would have been predictable to one of ordinary skill in the art, which is also applied to the instant invention. See KSR International Co. v. Teleflex Inc. 82 USPQ2d 1385 (2007).

In addition,

"The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.,* 325 U.S. 327, 65 USPQ 297 (1945)". See MPEP § 2144.07.

On p. 18-19 of the response, Applicant argues that neither Dodel nor Schenk provides clinical assessments including neurophysiological tests to observe the clinical outcome of immunotherapy. Applicant argues that the claimed invention is a better indicator of a positive clinical outcome in AD immunotherapy than the conventional ELISA method because high levels of immunoreactivity as determined by the claimed method show beneficial clinical effects as compared to the ELISA method. Applicant further cites Wang et al. and Sabamurti et al. in support of the arguments. Applicant's arguments have been fully considered but they are not persuasive.

In contrast, as previously made of record, both Dodel and Schenk teach methods of monitoring immunotherapy by detecting the level of anti-Abeta with an ELISA method. In addition, Schenk teaches image analysis on brains to determine amyloid-β burden after immunization with Abeta (p. 176), which is immunohistochemical analysis on the brain sections to monitor immunotherapy. Schenk further teaches that the reduction of Abeta accumulation in immunohistochemical analysis in animals immunized with Abeta peptides correlates with the increased levels of anti-Abeta and

the effect of anti-Abeta (see p. 176). Thus, both Dodel and Schenk's teach methods of detecting and assessing clinical outcome of immunotherapy of Abeta immunization.

Note that

"A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). See MPEP 716.02(a)-I.

Conclusion

9. NO CLAIM IS ALLOWED.

10. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday from 8:30 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/
Chang-Yu Wang, Ph.D.
December 15,2008

/Christine J Saoud/

Primary Examiner, Art Unit 1647